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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,679	10/30/2000	Evan C. Unger	UNGR-1598	8248
28213	7590	10/02/2007	EXAMINER	
DLA PIPER US LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133			SCHLIENTZ, LEAH H	
			ART UNIT	PAPER NUMBER
			1618	
			MAIL DATE	DELIVERY MODE
			10/02/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

09/699,679

Applicant(s)

UNGER ET AL.

Examiner

Leah Schlientz

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 25 June 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 3,4,12,13,17,22-35,61 and 63-81 is/are pending in the application.
- 4a) Of the above claim(s) 12 and 13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 3,4,17,22-35,61 and 63-81 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- ☐ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- ☐ Notice of Informal Patent Application
- ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/25/2007 has been entered.

### ***Status of Claims***

Claims 3, 4, 17 and 66 have been amended. Claims 3, 4, 12, 13, 17, 22 – 35, 61, and 63 – 81 are pending, of which claims 12 and 13 are withdrawn from consideration at this time as being drawn to a non-elected invention. Claims 3, 4, 17, 22 – 35, 61, and 63 – 81 are readable upon the elected invention and are examined herein on the merits for patentability.

The indicated allowability of claims 66 – 81 is withdrawn in view of further consideration of the prior art of record. Rejections based on the cited reference(s) follow.

### ***Response to Arguments***

Applicant's arguments, filed 6/25/2007, with respect to the rejection of claims 3, 4, 6 – 10, 17, 22 – 35, 61 and 63 – 65 under 35 USC 103(a) as being unpatentable over Unger *et al.* (WO 96/40285) have been fully considered but they are not persuasive for reasons set forth hereinbelow.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

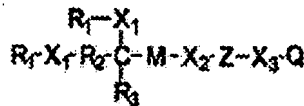
Claims 3, 4, 17, 22 – 35, 61, and 63 – 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger (WO 96/40285).

Unger discloses novel targeted compositions which may be used for diagnostic and therapeutic use, such as for therapeutic ultrasound (see abstract). Unger teaches

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that the composition can comprise a vesicle composition having an aqueous carrier, vesicles comprising a lipid and a gas, such as gas-filled liposomes (see page 4, lines 20 – 30, page 9, lines 15 – 25 and page 12, lines 25 – 33), and thus teaches a targeted vesicle composition for therapeutic or diagnostic use *in vivo* having an aqueous carrier and gas filled liposomes, as recited in claims 17 and 66. Unger further teaches that exemplary lipids that can be used to prepare the liposomes comprise phosphatidylcholines such as dioleoylphosphatidylcholine, dimyristoylphosphatidylcholine, and others (see page 23, lines 15 – 34).

Unger further teaches that the composition comprises a compound having the formula:



Where Q is a targeting ligand (see page 61, line 1 through page 62, line 33 and claim 136). It is noted that the compound as recited in claim 136 of Unger meets the limitation of the instant structure in that the carbon atom of the structure is linked to R<sub>2</sub>-X<sub>1</sub>-R<sub>1</sub> at one end and X<sub>1</sub>-R<sub>1</sub> at the other, and R<sub>3</sub> at the third position. Unger defines R<sub>2</sub> as being an alkylene moiety from 1-30 carbon atoms, which encompasses the instantly claimed species of R<sup>3</sup> as ethylene. Regarding the moieties R<sup>1</sup> and R<sup>4</sup> as recited in instant claims 17 or 66, Unger teaches that X<sub>1</sub> may be -C(=X)<sub>5</sub>-X<sub>4</sub>, where X<sub>5</sub> can be O, X<sub>4</sub> can be -NR<sub>4</sub>- and R<sub>4</sub> can be a hydrogen or alkyl of 1 – 10 carbon atoms, as in the instantly claimed structure wherein R<sup>2</sup> and R<sup>5</sup> are hydrogen lower alkyl, and thus

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teaches the moiety  $\text{-C(=O)-N(alkyl)-}$  that meets the limitation of the fragment  $\text{C(=O)-N(R}^2\text{)-}$ , as recited in claims 17 and 66. Regarding the acyl moieties  $\text{R}^1$  and  $\text{R}^4$ , Unger teaches that the alkyl group connected to  $\text{-C(=O)-N(alkyl)-}$  (and that thus forms an acyl group) can comprise an alkyl of 1 to 50 carbons, and thus teaches an acyl group that encompasses the claimed species of  $\text{R}^1$  that has from 16 to 23 carbons, including 18.  $\text{R}_3$  may be hydrogen.

Unger teaches a bond between the central carbon C and moiety M, and thus teaches  $\text{R}^6$  is a direct bond, as instantly claimed in claims 17 and 66. Regarding moiety  $\text{X}^1$  as recited in claims 17 and 66, Unger teaches that moiety M may be  $\text{-R}_5\text{-C(=X}_5\text{)-X}_4$ , where  $\text{R}_5$  can be a direct bond,  $\text{X}_5$  can be O, and  $\text{X}_4$  can be  $\text{NR}_4$ , with  $\text{R}_4$  being hydrogen or an alkyl from 1-10 carbon atoms. Thus Unger teaches that M can be the moiety  $\text{C(=O)-N(alkyl)-}$ , which meets the limitation of  $\text{X}^1$ , as instantly claimed. Unger teaches that  $\text{X}_2$  connected to M can be a direct bond, and moiety Z can be a hydrophilic polymer, which is preferably PEG (see page 62, lines 25 – 27 and claim 146).

Regarding the moieties  $\text{R}^7$  and  $\text{X}^2$ , as recited in claims 17 and 66, Unger teaches that a moiety  $\text{X}_3$  is present between the hydrophilic polymer, Z, and the peptide Q. Unger teaches that moiety  $\text{X}_3$  can be  $\text{-R}_5\text{-C(=X}_5\text{)-X}_4$ , wherein  $\text{R}_5$  is alkyl (preferably  $\text{C}_1$  or  $\text{C}_2$ ),  $\text{X}_5$  is O, and  $\text{X}_4$  is N, and thus teaches  $\text{X}_3$  can be  $\text{(alkyl)C(=O)-N-}$  (pages 61 – 64), which is directly overlapping in scope with instantly claimed portion of the compound  $\text{R}^7\text{-X}^2\text{-peptide}$ , wherein  $\text{R}^7$  is  $\text{CH}_2\text{CH}_2$ ,  $\text{X}_2$  is  $\text{C(=O)}$ , and N may be inherently donated from the targeting peptide via an amide bond in the instantly claimed structure.

Regarding the recitation in claims 17 and 66 that the targeting ligand T is a peptide having the sequence CRGDC, wherein the two cysteines are linked together via a disulfide linkage, Unger teaches that ligands useful for targeting the GPIIb/IIIa receptor include peptides flanked by cysteine residues that are capable of forming cyclic disulfides, such as cyclic, disulfide-bonded forms with the sequence Arg-Gly-Asp (i.e. RGD) (see page 57, lines 23 – 33 and page 55, lines 20 – 30), and thus teaches providing a peptide of sequence CRGDC as a targeting ligand for targeting the GPIIb/IIIa receptor.

Unger does not teach a specific embodiment of the compound having a combination of the specifically claimed targeting ligand that targets the GPIIb/IIIa receptor and the hydrophilic polymer, as in the elected species of compound.

However, it is considered that one of ordinary skill in the art at the time of the instant invention would have found it obvious to provide the compound that meets the limitation of formula (IV), as claimed and in particular, the elected species of such formula wherein the specific targeting ligand that targets the GPIIb/IIIa receptor and the hydrophilic polymer that is polyethylene glycol, because Unger teaches the compound having the structure that overlaps with and/or meets the limitations of the instant claims 17 and 66, and furthermore teaches that the compound can comprise targeting ligands that include the GPIIb/IIIa receptor as claimed and the polyethylene glycol hydrophilic polymer as claimed, and teaches such compounds are useful in a vesicle composition for diagnostic and therapeutic use. Accordingly, it is considered that one of ordinary skill in the art would have been motivated to provide the claimed compound with the

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expectation of providing a suitable compound for formulation in a vesicle composition for diagnostic use. Accordingly, claims 17 and 66 are obvious over the teachings of Unger et al.

Regarding claims 3, 4, 61 and 63, Unger teaches the compositions of the claims insofar as they read on the elected species, as discussed above.

Regarding claim 22 and 68, Unger teaches that the phosphatidylcholine provided in the composition can be dipalmitoylphosphatidylcholine (page 23, lines 15-34).

Regarding claims 23 – 24 and 69 – 70, Unger teaches that the lipids can comprise dipalmitoylphosphatidylethanolamine (page 23, lines 15-33). Regarding claims 25 and 71, Unger teaches that the lipids can comprise dipalmitoylphosphatidic acid (page 23, lines 15-34).

Regarding claims 26-29 and 72 – 75, Unger teaches that the vesicles can comprise a gas such as perfluorocarbon, including perfluoromethane, perfluoropropane, perfluorobutane, etc. (page 32, lines 3 –18). Regarding claims 30-33 and 76 – 79, Unger teaches the gas can be derived from a gaseous precursor such as perfluoropentane that is converted to a gas at 37 C (page 33, lines 16-33). The composition can also comprise bioactive agents such as urokinase, heparin, etc. (page 83, lines 9-24).

Regarding claims 64-65, the targeting ligand can comprise a peptide having the claimed number of amino acids, and can be cyclized (page 55, line 1 – page 59, line 20).



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Applicant argues, on page 12 of the Response that claim 17 as amended, now recites a general structure where "X is C(=O)," "R<sup>7</sup> is (CH<sub>2</sub>CH<sub>2</sub>)," and "P is PEG;" and that Unger fails to describe or suggest a composition that comprises a compound that satisfies all these limitations. Applicant contends that with respect to moiety X<sup>2</sup>, all that Unger teaches is the moiety C(=O)-N-alkyl, and with respect to the polymeric moiety, all that Unger teach is generic PEG.

This is non-persuasive because, regarding instantly claimed moiety X<sup>2</sup>, Unger teaches that moiety X<sub>3</sub> can be -R<sub>5</sub>-C(=X<sub>5</sub>)-X<sub>4</sub>, wherein R<sub>5</sub> is alkyl, X<sub>5</sub> is O, and X<sub>4</sub> is N, and thus teaches X<sub>3</sub> can be CH<sub>2</sub>CH<sub>2</sub>C(=O)-N- (pages 61 – 64), which is directly overlapping in scope with instantly claimed portion of the compound R<sup>7</sup>-X<sup>2</sup>-peptide, wherein R<sup>7</sup> is CH<sub>2</sub>CH<sub>2</sub>, X<sub>2</sub> is C(=O), and N may be inherently donated from the targeting peptide via an amide bond in the instantly claimed structure, as set forth above. Regarding PEG, all that is claimed with respect to moiety P is generic PEG.

### ***Conclusion***

No claims are allowed at this time.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LHS



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SUPERVISORY PATENT EXAMINER